FORM PTO-1390 (REV 10-95) | U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE | ATTORNEY'S DOCKET NUMBER: MERCK 2403

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. §371

U S APPLICATION NO. (If known, see 37 CFR §1 5): 10/089222

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/08373	28 AUGUST 2000	29 SEPTEMBER 1999

TITLE OF INVENTION: POROUS ORGANIC POLYMER MOULDINGS

APPLICANT(S) FOR DO/EO/US: MÜLLER, Egbert, et al

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ■ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. §371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C §371(b) and PCT Articles 22 and 39(1).
4. ■ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ■ A copy of the International Application as filed (35 U.S.C §371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau)
   b. ■ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ■ A translation of the International Application into English (35 U.S.C. §371(c)(2)).
7. ■ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ■ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. §371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 C.F.R. §§1 97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. §§3.28 and 3.31 is included.
13. ■ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

U.S. APPLICATION NO (if known, see 37 CFR §1 5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
10/089222	PCT/EP00/08373	MERCK 2403

17. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR §1.492 (a) (1) - (5)):		CALCULATIONS PTO USE ONLY
Search Report has been prepared by the EPO or JPO.....	$890.00	
International preliminary examination fee paid to USPTO (37 CFR §1.482).....	$710.00	
No international preliminary examination fee paid to USPTO (37 CFR §1.482) but international search fee paid to USPTO (37 CFR §1.445(a)(2)).....	$740.00	
Neither international preliminary examination fee (37 CFR §1.482) nor international search fee (37 CFR §1.445(a)(2)) paid to USPTO.....	$1040.00	
International preliminary examination fee paid to USPTO (37 CFR §1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....	$100.00	

ENTER APPROPRIATE BASIC FEE AMOUNT =	$890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(e)).		

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	8 - 20 =	0	x $ 18.00	$0.00	
Independent claims	1 - 3 =	0	x $ 84.00	$0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $ 280.00		
TOTAL OF ABOVE CALCULATIONS =				$890.00	
Reduction of 1/2 for filing by small entity, if applicable. A Verified Small Entity Statement must also be					
SUBTOTAL =				$890.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(f)).					
TOTAL NATIONAL FEE =				$890.00	
Fee for recording the enclosed assignment (37 C.F.R. §1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C F.R. §§3.28, 3.31). $40.00 per property.					
TOTAL FEES ENCLOSED =				$890.00	
				Amount to be refunded.	
				charged:	

a. ■ A check in the amount of $890.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 13-3402 in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ■ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-3402. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 C.F.R. §§1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. §1.137(a) or (b)) must be filed and granted to restore the application to pending status.

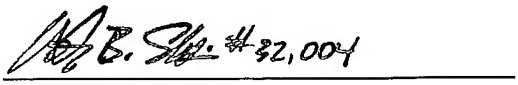
SEND ALL CORRESPONDENCE TO: Customer Number 23,599

23599

PATENT TRADEMARK OFFICE

Filed: 28 MARCH 2002

AJZ:kmo



SIGNATURE

Anthony J. Zelano

NAME

27,969

REGISTRATION NUMBER

IN THE UNITED STATES DESIGNATED/ELECTED OFFICE

International Application No.	:	PCT/EP00/08373
International Filing Date	:	28 AUGUST 2000
Priority Date(s) Claimed	:	29 SEPTEMBER 1999
Applicant(s) (DO/EO/US)	:	MÜLLER, Egbert, et al

Title: POROUS ORGANIC POLYMER MOULDINGS

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

SIR:

Prior to calculating the national fee, and prior to examination in the National Phase of the above-identified International application, please amend as follows:

IN THE CLAIMS:

3. (Amended) Process according to Claim 1, characterized in that a matrix moulding which has been modified with template molecules is used.

4. (Amended) Process according to Claim 1, characterized in that aqueous hydrofluoric acid is used for washing out the matrix moulding.

5. (Amended) Polymeric organic moulding which can be produced by the process corresponding to Claim 1.

7. (Amended) Chromatographic separating column, containing a moulding according to Claim 5.

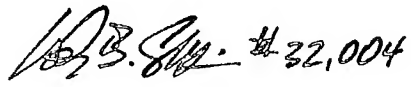
8. (Amended) Use of a moulding according to Claim 5 in the chromatographic separation of at least two substances.

REMARKS

The purpose of this Preliminary Amendment is to eliminate multiple dependent claims in order to avoid the additional fee. Applicants reserve the right to reintroduce claims to canceled combined subject matter.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version With Markings to Show Changes Made**".

Respectfully submitted,



Anthony J. Zelano, Reg. No. 27,969
Attorney for Applicants
MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
Arlington Courthouse Plaza 1
2200 Clarendon Boulevard, Suite 1400
Arlington, VA 22201
Direct Dial: 703-812-5311
Facsimile: 703-243-6410
Email: zelano@mwzb.com

AJZ:kmo

Filed: 28 MARCH 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 3 - 5, 7 and 8 were amended as follows:

3. (Amended) Process according to ~~one of~~ Claims 1 ~~and 2~~, characteriszed in that a matrix moulding which has been modified with template molecules is used.

4. (Amended) Process according to ~~one of~~ Claims 1 ~~and 3~~, characteriszed in that aqueous hydrofluoric acid is used for washing out the matrix moulding.

5. (Amended) Polymeric organic moulding which can be produced by the process corresponding to ~~one of~~ Claims 1 ~~to 4~~.

7. (Amended) Chromatographic sepearating column, containing a moulding according to ~~one of~~ Claims 5 ~~and 6~~.

8. (Amended) Use of a moulding according to ~~one of~~ Claims 5 ~~and 6~~ in the chromatographic sepearation of at least two substances.

Porous organic polymer mouldings

The invention relates to porous organic polymer mouldings which, owing to their properties, are particularly suitable as chromatographic separation materials, and to the production thereof by means of an imprinting process.

Polymeric mouldings are widely used as chromatographic separation materials. Known uses are of organic polymeric membranes for the separation of macromolecular substances (EP 0 320 023) and of porous silica gel mouldings instead of the conventional particulate sorbents for chromatographic separations (WO 95/03256). Silica gel mouldings can be produced with a defined narrow pore distribution. Through the combination of mesopores and macropores, good separation efficiencies can be achieved, even at a high flow rate. In this way, mouldings offer more advantageous properties than particulate support materials.

However, a disadvantage of silica gel mouldings is their inadequate stability in aqueous eluents, in particular at pH values > 7. For this reason, they cannot be employed for all chromatographic separation methods, such as, for example, ion exchange chromatography. Furthermore, there are restrictions in the purification and antifouling treatment of silica gel-based sorbents.

By contrast, mouldings made from organic materials would have suitable stability, but to date cannot be produced in the same quality as inorganic mouldings produced by the sol-gel process (WO 95/03256). Membranes made from organic polymers can be produced by bulk polymerisation in the presence of a porogen (EP 0 320 023). These polymer membranes are preferably used for the separation of macromolecular substances, such as biopolymers, since macroporous materials can be used for applications of this type. However, mesoporous organic polymers having a nar-

row pore distribution for the separation of smaller molecules cannot be produced in the requisite quality.

EP 0 366 252 describes the production of porous organic support materials by a polymeric impression of silica gel particles. The pore system of the silica gel particles is filled with polymer by suspension polymerisation, and monomer and initiator are removed by extraction. A disadvantage in this process is the need for phase separation. In addition, the process merely offers the possibility of producing particulate support materials.

The object of the present invention was therefore to find a simple production process which enables the production of polymer mouldings having a large specific surface area and a defined pore structure. Materials of this type are particularly suitable for the chromatographic separation of components of low molecular weight.

It has been found that organic polymer mouldings for chromatography can be produced by bulk polymerisation of monomers in a silica gel moulding followed by removal of the silica gel by dissolution. These polymer mouldings exhibit separation efficiencies which are equivalent to those of silica gel mouldings.

The present invention accordingly relates to a process for the production of polymeric organic mouldings, characterised by the following process steps:

a) provision of a moulding as matrix;
b) filling of the cavities of the moulding with a monomer solution;
c) polymerisation of the monomer solution;
d) removal of the matrix moulding by washing out and dissolution.

In a preferred embodiment, the matrix moulding used is a silica gel moulding.

In a preferred embodiment, a matrix moulding which has been modified with template molecules is used.

In a further preferred embodiment, aqueous hydrofluoric acid is used for washing out the matrix moulding.

The present invention also relates to polymeric organic mouldings obtainable by

a) provision of a moulding as matrix;
b) filling of the cavities of the moulding with a monomer solution;
c) polymerisation of the monomer solution;
d) removal of the matrix moulding by washing out and dissolution.

In a preferred embodiment, the surfaces of the mouldings have separation effectors.

The present invention also relates to a chromatographic separating column which contains a moulding according to the invention.

The present invention also relates to the use of a moulding according to the invention in the chromatographic separation of at least two substances.

For the purposes of the present invention, organic polymeric mouldings are mouldings of any shape, for example membranes or flat or column-shaped mouldings. Flat mouldings have their greatest dimension transverse to the flow direction of the eluent. Particular preference is given to mouldings, such as column-shaped mouldings, which have a dimension of equal length or longer along the axis through which the eluents flow. The size and dimension of the mouldings correspond to the usual dimensions for use in chromatography. Flat mouldings typically have a thickness of

between 0.2 and 20 µm, column-shaped mouldings typically have a diameter of between 0.1 cm and 5 cm and a length (longest dimension) of between 1 and 30 cm. For preparative separations, the stated dimensions can be exceeded in accordance with the dimensions of known column dimensions. For miniaturised applications, the stated dimensions can be reduced into the region of capillaries.

For the purposes of the present invention, organic polymeric mouldings are also mouldings which can be used for a radial column. In this case, the flow through the moulding does not take place along its longitudinal axis. Instead, it has a hole along the longitudinal axis through which the eluent firstly enters the moulding and subsequently exits radially at the periphery. The depth and diameter of the hole depend on the dimensions of the moulding and have the usual magnitude for applications of this type.

Matrix mouldings which are used for the process according to the invention are typically porous mouldings of corresponding dimensions whose pore system is formed, in particular, from macropores. The mouldings preferably additionally also have mesopores in the walls of the macropores. The interconnected macropores typically have a diameter which has a median value of greater than 0.1 µm. The diameter of the mesopores generally has a median value of between 2 and 100 nm. The porosity and specific surface area of the polymerised moulding can be affected by the type of porosity and specific surface area respectively of the matrix moulding. The mouldings according to the invention which are formed may accordingly have macropores and preferably also mesopores having a size in the same order as stated for the matrix mouldings.

Instead of a porous moulding, the matrix moulding used may alternatively be a column or a corresponding holder which is filled with porous particles. In this case, the particle interspaces usually form macropores.

In order to be able to remove the matrix moulding when the polymerisation is complete, the former must be dissolved and washed out without destroying the organic polymer formed. Matrix mouldings made from inorganic materials, such as inorganic oxides, particularly preferably silica gel, are therefore preferably used. These may be, for example, monolithic mouldings, as described in WO 94/19687 or WO 95/03256. They may be employed in calcined or uncalcined form, depending on the desired porosity of the organic polymer to be prepared.

Matrix mouldings made from silica gel can be washed out with aqueous bases or, particularly preferably, with aqueous hydrofluoric acid. If the polymerised organic mouldings are likewise labile under such conditions, another matrix moulding has to be selected. This may be, for example, a porous matrix moulding made from an organic polymer which is washed out under conditions which do not destroy the polymerised moulding. Thus, for example, polylactides or melamine-phenol-formaldehyde resins can be employed.

The process according to the invention enables the production of an extremely wide variety of organic polymeric mouldings. The mouldings can be produced, for example, by free-radical, ionic or thermal polymerisation. These may be, for example, poly(meth)acrylic acid derivatives, polystyrene derivatives, polyesters, polyamides or polyethylenes. The monomers correspondingly to be employed are known to the person skilled in the art in the area of organic polymers. For example, these are monoethylenically or polyethylenically unsaturated monomers, such as vinyl monomers, vinylaromatic and vinylaliphatic monomers, for example styrene and substituted styrenes, vinyl acetates or vinyl propionates, acrylic monomers, such as methacrylates and other alkyl acrylates, ethoxymethyl acrylate and higher analogues, and the corresponding methacrylic acid esters or amides thereof, such as acrylamide, or acrylonitrile. Further monoethyleni-

cally and polyethylenically unsaturated monomers are given, for example, in EP 0 366 252 or US 5,858,296.

The person skilled in the art is able correspondingly to combine the various monomers, where appropriate to select a suitable free-radical starter or initiator and thus to put together a monomer solution with which the matrix moulding is filled. The polymerisation duration and temperature are matched to the respective monomer solution in accordance with conventional rules.

After completion of the polymerisation step, the solid moulding produced, which consists, for example, of the inorganic matrix polymer and the cast organic polymer, is removed, and the material of the matrix moulding is washed out and dissolved out. To this end, the moulding is stored or preferably swirled in a wash solution, optionally with heating. Treatment with aqueous hydrofluoric acid in order to remove silica gel typically takes 48 hours.

After further washing steps in order to remove the aggressive wash solution and final particles, the porous organic polymeric moulding is obtained as an impression or counterpart to the matrix moulding employed.

If the mouldings produced already have the suitable functionalities, they can be employed directly for chromatographic separations. For example, a polymer made from polystyrene or derivatives thereof can be used directly for reversed phase separations. To this end, the mouldings are provided with corresponding connectors, surrounded by a casing and integrated into a chromatographic separating column. Suitable holders and casings are already known for inorganic monolithic sorbents (for example WO 98/59238 and the unpublished DE 99 32 318) and can be applied to the mouldings according to the invention. Particularly in the case of encasing with plastics, such as, for example, PEEK or fibre-reinforced PEEK,

the organic mouldings according to the invention can usually be encased more effectively and in a more leak-proof manner than the corresponding inorganic mouldings, since they are able to undergo stronger binding to the plastic casing.

Depending on the separation properties that the moulding according to the invention is to have, however, further modifications may first be necessary. For example, if it is to be employed for affinity or ion-exchange chromatography, the surface must be provided with corresponding separation effectors. In some cases, suitable substances may already have been added to the monomer solution and thus incorporated directly into the polymer. Preferably, however, functionalities are firstly introduced during the polymerisation in accordance with known processes and can subsequently be reacted with separation effectors. Further modification can likewise be introduced onto the polymeric mouldings by block or graft polymerisation. Separation effectors and monomers which, besides a polymerisable double bond, also contain further functionalities, such as, for example, oxirane rings, are known to the person skilled in the art. Examples are given in WO 96/2216, WO 96/22316 and WO 95/10354.

Suitable functionalities of the mouldings according to the invention can likewise be used to bind or immobilise biomolecules, such as, for example, enzymes. Macroporous mouldings are particularly suitable for this purpose. Biomolecules, such as, for example, enzymes, therefore also come under the term separation effectors in accordance with the invention.

The process according to the invention furthermore enables the production of mouldings having particular separation properties. As in molecular imprinting, template molecules can be bound to the surface of the matrix moulding, which in this case is porous or nonporous. The interspaces or pores are subsequently filled with monomer solution and polymerised to completion. During the polymerisation, cavities form around the template

molecules. The matrix moulding and the template molecules bound thereto are then washed out. In contrast to the known processes of molecular imprinting, the process according to the invention offers the advantage that, due to the binding to the matrix moulding, the template molecules adopt a position of defined alignment. This results in the formation of cavities which are more defined and are able to undergo clearer and stronger interactions during the chromatographic separation. A further major advantage of the process according to the invention is that all template molecules can be washed out after the polymerisation.

In conventional processes, some of the template molecules are completely surrounded by the polymer after the polymerisation and can only be removed from the polymer very slowly or not at all. Since template molecules can also be liberated from the polymer during later use of the polymers for chromatographic separation and falsify the analysis, the use of such materials is usually restricted to purification or qualitative analysis. Trace analysis is virtually impossible.

Polymers prepared in accordance with the invention do not exhibit this bleeding. The reason for this is the preferably covalent bonding of the template molecules to the matrix moulding. In this way, they are never completely surrounded and held by the polymerised moulding, but instead are completely removed together with the matrix moulding by the washing-out of the latter.

In addition, the preparation of an imprint polymer in accordance with the prior art requires a large amount of purified template, which can only be recovered again with difficulty. In the process according to the invention, by contrast, the template is firstly bonded to the matrix moulding. Excess template molecules can be washed off and collected. It is not until a second step that the monomer solution is added and polymerised. The polymer mouldings produced by the process according to the invention using a

template can be both employed as mouldings or, for certain applications, subsequently comminuted to give particles.

The process according to the invention thus offers the possibility of producing organic polymeric mouldings of defined porosity. The pores can be defined by the matrix moulding itself or by modification of the matrix moulding with template molecules. The materials according to the invention enable at least equivalent separation efficiencies to be achieved compared with particulate sorbents and do so at a higher flow rate. Both the surface of the matrix moulding and the surface of the moulding according to the invention can be modified, so that there is a multiplicity of ways of matching the mouldings ideally to the respective separation problem.

Even without further details, it is assumed that a person skilled in the art will be able to utilise the above description in its broadest scope. The preferred embodiments and examples should therefore merely be regarded as descriptive disclosure which is absolutely not limiting in any way.

The complete disclosure content of all applications, patents and publications listed above and below, in particular the corresponding application DE 199 46 674, filed on 29.09.1999, is incorporated into this application by way of reference.

Examples

1. Production of a polymer moulding using a silica gel matrix moulding

Material:
4 uncalcined silica gel matrix mouldings (length 11 cm, ∅ 4 mm)
monomer solution consisting of: 35 ml of styrene, 35 ml of divinylbenzene (destabilised with NaOH and dried with Na_2SO_4) and
0.7 g of azoisobutyronitrile

Equipment:
100 ml single-necked flask,
2 dropping funnels with pressure equalisation
drying oven with rotation device

Procedure:
The silica gel matrix mouldings are introduced into a 250 ml dropping funnel lying crosswise and evacuated for 10 minutes. The monomer solution is added dropwise over the course of 2 minutes under reduced pressure. After 10 minutes, when bubble formation is no longer evident, the supernatant polymer solution is poured off, and the mouldings are introduced into the rotary oven, where the polymerisation is carried out at 70°C for 20 hours. After cooling, the parts are introduced into 50% aqueous (v:v) hydrofluoric acid and shaken for 2 days.
They are subsequently washed with water and 0.5 M phosphate buffer (pH 5.5).
The organic mouldings produced are then extracted in each case for 6 hours with toluene and acetonitrile. The mouldings are subsequently inserted into a shrink tube and encapsulated with epoxy resin, with HPLC connectors being cast in at the same time.

Polymer moulding data:
mean pore size: 12.2 nm
pore volume: 0.16 cm^3
mean specific surface area: 50 m^2 (determined by the BET method)

Chromatographic test:

The number of theoretical plates was determined with toluene:
eluent: acetonitrile/water, 60:40
wavelength: 254 nm

Number of theoretical plates: 9935 theoretical plates per m

2. Production of a polymer moulding as impression of a column packed with silica gel particles

Procedure:
Monospherical silica gel particles (diameter 2 µm) were packed into a Superformance column 50 – 10.
In each case, 10 ml of styrene, 10 ml of divinylbenzene and 0.2 g of AIBN were introduced and reacted at 70°C. After the reaction, the product was removed and introduced into 50% (v:v) HF solution. The product was subsequently washed with water, phosphate buffer (pH 5.5) (in each case 1 hour and 50 ml), methanol, acetone and acetonitrile (100 ml, 10 hours each).

Claims

1. Process for the production of polymeric organic mouldings, characterised by the following process steps:

a) provision of a moulding as matrix

b) filling of the cavities of the moulding with a monomer solution

c) polymerisation of the monomer solution

d) removal of the matrix moulding by washing out and dissolution

2. Process according to Claim 1, characterised in that the matrix moulding used is a silica gel moulding.

3. Process according to one of Claims 1 and 2, characterised in that a matrix moulding which has been modified with template molecules is used.

4. Process according to one of Claims 1 to 3, characterised in that aqueous hydrofluoric acid is used for washing out the matrix moulding.

5. Polymeric organic moulding which can be produced by the process corresponding to one of Claims 1 to 4.

6. Polymeric organic moulding according to Claim 5, characterised in that the surface of the moulding has separation effectors.

7. Chromatographic separating column, containing a moulding according to one of Claims 5 and 6.

8. Use of a moulding according to one of Claims 5 and 6 in the chromatographic separation of at least two substances.

Abstract

The invention relates to porous organic polymer mouldings which, owing to their properties, are particularly suitable as chromatographic separation materials, and to the production thereof by means of an imprinting process. To this end, polymerisation is carried out in a matrix moulding, and the matrix moulding is subsequently removed by washing out.

Docket No.
Merck

Declaration and Power of Attorney For Patent Application
English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Porous organic polymer mouldings

the specification of which

(check one)

☐ is attached hereto.
☒ was filed on 28.09.2000 as United States Application No. or PCT International Application Number PCT/EP00/08373
and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
199 46 674.2 (Number)	German (Country)	29.09.1999 (Day/Month/Year Filed)	☐
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	☐
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U.S.C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States of PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112. I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C.F.R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

(16)

POWER OF ATTORNEY: As a named inventor, I hereby appoint

I. William Millen (Reg. No. 19,544)
John L. White (Reg. No. 17,746)
Anthony J. Zelano (Reg. No. 27,969)
Alan E.J. Branigan (Reg. No. 20,565)
John R. Moses (Reg. No. 24,983)
Harry B. Shubin (Reg. No. 32,004)
Brion P. Heaney (Reg. No. 32,542)
Richard J. Traverso (Reg. No. 30,595)
John A. Sopp (Reg. No. 33,103)
Richard M. Lebovitz (Reg. No. 37,067)
John H. Thomas (Reg. No. 33,460)
Catherine M. Joyce (Reg. No. 40,668)
James T. Moore (Reg. No. 35,619)
James E. Ruland (Reg. No. 37,432)
Nancy Axelrod (Reg. No. 44,014)
Jennifer J. Branigan (Reg. No. 40,921)

to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

Send Correspondence to: MILLEN; WHITE; ZELANO & BRANIGAN, P.C.
Arlington Courthouse Plaza I
2200 Clarendon Blvd., Suite 1400
Arlington, VA 22201

Direct Telephone Calls to: (name and telephone number)

1-00

Full name of sole or first inventor	
MÜLLER, Egbert	29.04.2002
Sole or first inventor's signature: E. Müller	Date
Residence: Im Erlich 10, 64291 Darmstadt, Germany DEX	
Citizenship: German	
Post Office Address: c/o Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany	

2-00

Full name of second inventor, if any	
SCHÄFER, Chris	29.04.2002
Second inventor's signature: X C. Schäfer	Date
Residence: Müllerstraße 19, 64289 Darmstadt, Germany DEX	
Citizenship: German	
Post Office Address: c/o Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany	

3-dv

Full name of third inventor, if any
LUBDA, Dieter 29.04.2002
Third inventor's signature Date
Residence
Im Bangert 21c, 64625 Bensheim, Germany DEX
Citizenship
German
Post Office Address
c/o Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany

Full name of fourth inventor, if any
Fourth inventor's signature Date
Residence
Citizenship
Post Office Address

Full name of fifth inventor, if any
Fifth inventor's signature Date
Residence
Citizenship
Post Office Address

Full name of sixth inventor, if any
Sixth inventor's signature Date
Residence
Citizenship
Post Office Address